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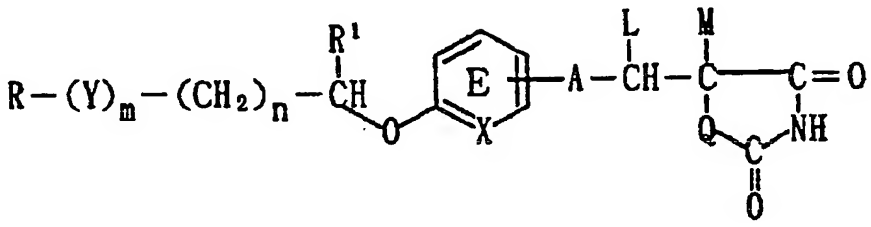

(I)

(57) Abstract

An anti–inflammatory agent which affects by way of a TNF–α inhibitory action and comprises a compound of formula (I) wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula –CO–, –CH(OH)–, or –NR^3– where R^3 represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R^1 represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R^1; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond or a salt thereof.

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DESCRIPTION
ANTI-INFLAMMATORY AGENT

TECHNICAL FIELD

The present invention relates to an anti-inflammatory agent which is useful as an agent for prophylaxis and treatment of a TNF(Tumor Necrosis Factor)-α mediated inflammatory disease.

BACKGROUND ART

Regarding a relationship between TNF-α and a thiazolidine derivative, the following references 1) to 4) are known.

1) JP-A H7(1995)-285864 describes that a thiazolidine derivative inhibits production and response reaction of TNF.

2) Saishin-Igaku, Vol. 52, No.6, pp.95-102 (1997) describes that a thiazolidine derivative reduces expression of TNF-α and improves insulin-resistance caused by TNF-α.

3) Endocrinology, Vol. 134, No. 1, pp.264-270 (1994) describes that the overexpression of mRNA for TNF-α and both of its receptors are at least partly normalized by treatment of the diabetic animals with the insulin-sensitizing agent pioglitazone.

4) Endocrinology, Vol. 136, No. 4, pp.1474-1481 (1995) describes that insulin-sensitizing agents exert their antidiabetic activities by antagonizing the inhibitory effects of TNF-α.

While, regarding a relationship between an inflammatory disease and a thiazolidine deivative, the following references 5) and 6) are known.

5) WO 96/34943 describes a method for treating a cytokine mediated autoimmune, inflammatory or atherosclerotic disorder with a human 12-lipoxygenase inhibitor. The human 12-lipoxygenase inhibitor is exemplified by pioglitazone, namely 5-[4-[2-(5-ethyl-2-

pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.
6) The Journal of Biological Chemistry, Vol.271, No.23, pp.13515-13522 (1996) describes that a thiazolidinedione related compound such as 1-(3-allyl-4-oxothiazolidine-2-yliden)-4-methylthiosemicarbazone exhibits antiarthritic activity.

However, none of the above references describes that a thiazolidine derivative is useful as an agent for prophylaxis and treatment of a TNF-α mediated inflammatory disease.

An inflammatory reaction includes various acute and chronic reactions which occur when stimulation was added to the living body. Such reactions include unfavorable reactions which cause destruction of the living tissues as well as favorable reactions to the living body with the purpose of excluding the alien substance. So far, inflammatory diseases are treated with steroid or a nonsteroidal anti-inflammatory agent, an immunosuppressive agent, and the like. However, such agents have problems that they inhibit favorable reactions as well as unfavorable reactions at the time of inflammation. Therefore, agents which inhibit only unfavorable reactions to the living body are desired.

It is thought that various cytokines are produced to regulate inflammation reactions at the time of inflammation. TNF-α which is one of such cytokines is thought to play an important role in expansion and delay of inflammation. For instance, it is thought that production of TNF-α increased to cause destruction of articular tissues in rheumatoid arthritis which belongs to an inflammatory disease.

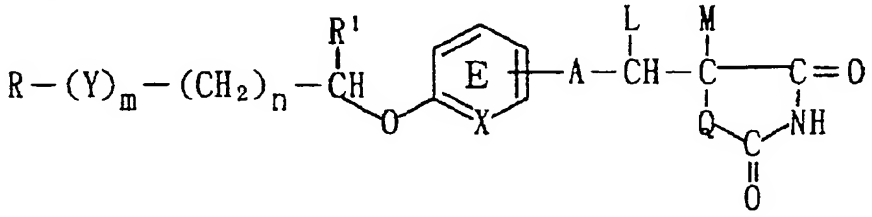
Based on the above situations, agents which specifically inhibit TNF-α mediated inflammation reactions are expected to be an anti-inflammatory agent with reduced side effects, therefore development of such

agents are desired.

DISCLOSURE OF INVENTION

The present invention relates to

(1) An anti-inflammatory agent which affects by way of a TNF-α inhibitory action and comprises a compound of the formula:



wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula -CO-, -CH(OH)-, or $-NR^3-$ where R^3 represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R^1 represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R^1; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond; or a salt thereof (hereinafter referred to simply as Compound (I));

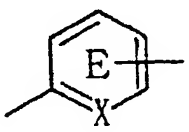
(2) An anti-inflammatory agent according to the above (1), wherein the heterocyclic group represented by R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen in addition to carbon as ring members or a condensed heterocyclic group;

(3) An anti-inflammatory agent according to the above (1), wherein R represents a heterocyclic group that may be substituted;

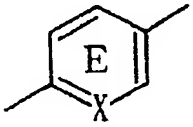
(4) An anti-inflammatory agent according to the above (3),

wherein the heterocyclic group is pyridyl, oxazolyl or thiazolyl;

(5) An anti-inflammatory agent according to the above (1), wherein the partial structural formula:



is the formula:



(6) An anti-inflammatory agent according to the above (1), wherein X represents CH;

(7) An anti-inflammatory agent according to the above (1), wherein R^1 represents hydrogen;

(8) An anti-inflammatory agent according to the above (1), wherein L and M respectively represent hydrogen;

(9) An anti-inflammatory agent according to the above (1), wherein the compound is 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione;

(10) An anti-inflammatory agent according to the above (1), wherein the compound is (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione;

(11) Method for treating or preventing a TNF-α mediated inflammatory disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound as defined in the above (1) or a pharmacologically acceptable salt thereof; and

(12) Use of a compound as defined in the above (1) or a pharmacologically acceptable salt thereof for the manufacture of an agent for prophylaxis or treatment of a TNF-α mediated inflammatory disease.

Referring to the hydrocarbon group that may be substituted for R, the hydrocarbon group includes aliphatic, alicyclic, alicyclic-aliphatic, aromatic-aliphatic, and aromatic hydrocarbon groups. The number of carbon atoms constituting such hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon group is preferably a C_{1-8} aliphatic hydrocarbon group. The aliphatic hydrocarbon group includes saturated C_{1-8} aliphatic hydrocarbon groups (e.g. alkyl groups) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, isohexyl, heptyl, and octyl; and unsaturated C_{2-8} aliphatic hydrocarbon groups (e.g. alkenyl, alkadienyl, alkynyl, and alkadiynyl groups) such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, and 1-octynyl.

The alicyclic hydrocarbon group is preferably a C_{3-7} alicyclic hydrocarbon group. The alicyclic hydrocarbon group includes saturated C_{3-7} alicyclic hydrocarbon groups (e.g. cycloalkyl groups) such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. and unsaturated C_{5-7} alicyclic hydrocarbon groups (e.g. cycloalkenyl groups and cycloalkadienyl groups) such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, and 2,4-cycloheptadienyl.

The alicyclic-aliphatic hydrocarbon group is a group consisting of the above-described alicyclic hydrocarbon group and aliphatic hydrocarbon group (e.g. cycloalkyl-alkyl and cycloalkenyl-alkyl groups) and is preferably a C_{4-9} alicyclic-aliphatic hydrocarbon group. Specifically, the alicyclic-aliphatic hydrocarbon group includes cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-

cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, cycloheptylethyl, etc.

The aromatic-aliphatic hydrocarbon group is preferably a C_{7-13} aromatic-aliphatic hydrocarbon group (e.g. aralkyl and aryl-alkenyl groups). The aromatic-aliphatic hydrocarbon group includes C_{7-9} phenylalkyl such as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl; C_{11-13} naphthylalkyl such as α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl, and β-naphthylethyl; C_{8-10} phenylalkenyl such as styryl and 4-phenyl-1,3-butadienyl; and C_{12-13} naphthylalkenyl such as 2-(2-naphthyl)vinyl.

The aromatic hydrocarbon group is preferably a C_{6-14} aromatic hydrocarbon group (e.g. aryl groups). The aromatic hydrocarbon group includes phenyl and naphthyl (α-naphthyl, β-naphthyl).

Referring to the formula (I), the heterocyclic group in a heterocyclic group that may be substituted for R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members or a condensed heterocyclic group. The condensed heterocyclic group may for example be one consisting of such a 5- to 7-membered monocyclic and heterocyclic group and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring, or a 5-membered ring containing one sulfur atom.

Specifically the heterocyclic group includes 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl,

indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl, benzopyranyl and 3,4-dihydrobenzopyran-2-yl. The preferred heterocyclic group is pyridyl, oxazolyl, or thiazolyl.

Referring to the formula (I), the hydrocarbon group and heterocyclic group for R may respectively have 1 to 5, preferably 1 to 3 substituents at substitutable positions. Such substituents include for example aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen, nitro, amino group that may be substituted, acyl groups that may be substituted, hydroxy group that may be substituted, thiol that may be substituted, and carboxyl group that may be esterified.

The aliphatic hydrocarbon group includes straight-chain or branched aliphatic hydrocarbon groups having 1 to 15 carbon atoms, such as alkyl groups, alkenyl groups, and alkynyl groups.

The preferred alkyl group is a C_{1-10} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl, and decyl.

The preferred alkenyl group is a C_{2-10} alkenyl group, such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

The preferred alkynyl group is a C_{2-10} alkynyl group, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl,

and 5-hexynyl.

The alicyclic hydrocarbon group includes saturated and unsaturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms, such as cycloalkyl groups , cycloalkenyl groups, and cycloalkadienyl groups.

The preferred cycloalkyl group is a C_{3-10} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, and bicyclo[4.3.1]decyl.

The preferred cycloalkenyl group is a C_{3-10} cycloalkenyl group, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, and 3-cyclohexen-1-yl.

The preferred cycloalkadienyl group is a C_{4-10} cycloalkadienyl group, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl.

The term "aryl group" means a monocyclic or condensed polycyclic aromatic hydrocarbon group. As preferred examples, C_{6-14} aryl groups such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl can be mentioned. Particularly preferred are phenyl, 1-naphthyl, and 2-naphthyl.

The preferred aromatic heterocyclic group includes 5- to 7-membered monocyclic aromatic heterocyclic groups containing 1 to 4 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members, such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl; and bicyclic or tricyclic condensed aromatic

heterocyclic groups containing 1 to 5 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members, such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, and 1,2,4-triazolo[4,3-b]pyridazinyl.

The preferred non-aromatic heterocyclic group includes oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, and morpholino.

The halogen includes fluorine, chlorine, bromine, and iodine, and is preferably fluorine or chlorine.

The amino group that may be substituted includes amino ($-NH_2$) that may be mono- or di-substituted by, for example, C_{1-10} alkyl groups, C_{3-10} cycloalkyl groups, C_{2-10} alkenyl groups, C_{3-10} cycloalkenyl groups, C_{1-13} acyl groups (e.g. C_{2-10} alkanoyl groups, C_{7-13} arylcarbonyl groups), or C_{6-12} aryl groups. As examples of the substituted amino group, there can be mentioned methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, acetylamino, propionylamino, benzoylamino, phenylamino, and N-methyl-N-phenylamino.

The acyl group in the acyl groups that may be substituted includes C_{1-13} acyl groups. For example, formyl

and groups formed between carbonyl and C_{1-10} alkyl groups, C_{3-10} cycloalkyl groups, C_{2-10} alkenyl groups, C_{3-10} cycloalkenyl groups, C_{6-12} aryl groups, or aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl). The preferred acyl group includes acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, and nicotinoyl. The substitutent in the substituted acyl groups includes C_{1-3} alkyl, C_{1-3} alkoxy groups, halogen (e.g. chlorine, fluorine, bromine, etc.), nitro, hydroxy, and amino.

Referring to the hydroxy group that may be substituted, the substituted hydroxy includes alkoxy, alkenyloxy, aralkyloxy, acyloxy, and aryloxy groups.

The preferred alkoxy group includes C_{1-10} alkoxy groups, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy, and cyclohexyloxy.

The preferred alkenyloxy group includes C_{2-10} alkenyloxy groups, such as allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, and 2-cyclohexenylmethoxy.

The preferred aralkyloxy group includes C_{7-10} aralkyloxy groups, such as phenyl-C_{1-4} alkyloxy (e.g. benzyloxy, phenethyloxy, etc.).

The preferred acyloxy group includes C_{2-13} acyloxy groups, more preferably C_{2-4} alkanoyloxy (e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.).

The preferred aryloxy group includes C_{6-14} aryloxy groups, such as phenoxy, and naphthyloxy. This aryloxy group may have 1 or 2 substituents such as halogen (e.g. chlorine, fluorine, bromine, etc.). The substituted aryloxy group includes 4-chlorophenoxy.

Referring to the thiol group that may be substituted, the substituted thiol group includes alkylthio, cycloalkylthio, aralkylthio, and acylthio groups.

The preferred alkylthio group includes C_{1-10} alkylthio groups, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, and nonylthio. The preferred cycloalkylthio group includes C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio, and cyclohexylthio.

The preferred aralkylthio group includes C_{7-10} aralkylthio groups, such as phenyl-C_{1-4} alkylthio (e.g. benzylthio, phenethylthio, etc.).

The acylthio group is preferably a C_{2-13} acylthio group, more preferably a C_{2-4} alkanoylthio group (e.g. acetylthio, propionylthio, butyrylthio, isobutyrylthio, etc.).

The carboxyl group that may be esterified includes alkoxycarbonyl, aralkyloxycarbonyl, and aryloxycarbonyl groups.

The preferred alkoxycarbonyl group includes C_{2-5} alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl.

The preferred aralkyloxycarbonyl group includes C_{8-10} aralkyloxycarbonyl groups, such as benzyloxycarbonyl.

The preferred aryloxycarbonyl group includes C_{7-15} aryloxycarbonyl groups, such as phenoxycarbonyl, and p-tolyloxycarbonyl.

The preferred substituent on the hydrocarbon or heterocyclic group for R includes C_{1-10} alkyl groups, aromatic heterocyclic groups, and C_{6-14} aryl groups. Particularly preferred is C_{1-3} alkyl, furyl, thienyl, phenyl, or naphthyl.

Referring to the formula (I), when the substituent on the hydrocarbon or heterocyclic group for R is an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic

group, or a non-aromatic heterocyclic group, this substituent may be further substituted by one or more, preferably 1 to 3 suitable substituents. As such substituents, there can be mentioned C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups (e.g. phenyl, naphthyl, etc.), aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl, thiazolyl, etc.), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino, piperazino, etc.), C_{7-9} aralkyl groups, amino, N-mono(C_{1-4})alkylamino groups, N,N-di(C_{1-4})alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino, benzoylamino, etc.), amidino, C_{2-8} acyl groups (e.g. C_{2-8} alkanoyl groups, etc.), carbamoyl, N-mono(C_{1-4})alkylcarbamoyl groups, N,N-di(C_{1-4})alkylcarbamoyl groups, sulfamoyl, N-mono(C_{1-4})alkylsulfamoyl groups, N,N-di(C_{1-4})alkylsulfamoyl groups, carboxyl, C_{2-8} alkoxycarbonyl groups, hydroxy, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups (e.g. phenyloxy, naphthyloxy, etc.), mercapto, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups, C_{6-14} arylthio groups (e.g. phenylthio, naphthylthio, etc.), sulfo, cyano, azido, nitro, nitroso, and halogen (e.g. fluorine, chlorine, bromine, iodine).

In the formula (I), R is preferably a heterocyclic group that may be substituted. More preferably, R is pyridyl, oxazolyl, or thiazolyl group, which may have 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl, and naphthyl.

Referring to the formula (I), Y represents -CO-, -CH(OH)- or -NR^3-. Y is preferably -CH(OH)- or -NR^3- and more preferably -CH(OH)-. Referring to an alkyl group that may be substituted for R^3, the alkyl group includes C_{1-4} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and t-butyl. The substituent includes halogen (e.g. fluorine, chlorine, bromine,

iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy), hydroxy, nitro, and C_{1-4} acyl groups (e.g. formyl, acetyl, propionyl, etc.).

The symbol m represents 0 or 1 and is preferably 0.

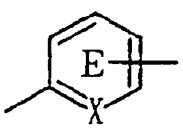
The symbol n represents 0, 1 or 2 and is preferably 0 or 1.

The symbol X represents CH or N and is preferably CH.

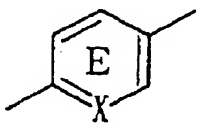
Referring to the formula (I), the symbol A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms. This aliphatic hydrocarbon group may be straight-chain or branched and may further be saturated or unsaturated. Thus, for example, $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_2-$, $-CH(C_2H_5)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, etc. can be mentioned for the saturated bivalent aliphatic hydrocarbon group, while $-CH=CH-$, $-C(CH_3)=CH-$, $-CH=CH-CH_2-$, $-C(C_2H_5)=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-CH_2-$, $-CH=CH-CH=CH-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH_2-$, etc. can be mentioned for the unsaturated bivalent aliphatic hydrocarbon group. The symbol A preferably represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, which is preferably a saturated group. More preferably, A represents a chemical bond, $-CH_2-$ or $-(CH_2)_2-$. Still more preferably, A represents a chemical bond or $-(CH_2)_2-$.

The alkyl group for R^1 includes C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and t-butyl. Preferably, R^1 represents hydrogen.

Referring to the formula (I), the partial structural formula:



is preferably the formula:



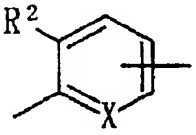
wherein each symbols has the same meanings as defined above.

Furthermore, ring E may optionally have 1 to 4

substituents at substitutable positions. Such substituents include an alkyl group, a hydroxy group that may be substituted, halogen, an acyl group that may be substituted, nitro, and an amino group that may be substituted. These substituents may be the same as the substituents mentioned for the hydrocarbon or heterocyclic group for R.

Ring E, the partial structural formula:

is preferably the formula:

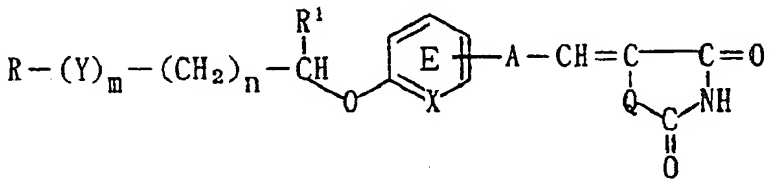


wherein R^2 represents hydrogen, an alkyl group, a hydroxy group that may be substituted, halogen, an acyl group that may be substituted, nitro, or an amino group that may be substituted.

The alkyl group, hydroxy group that may be substituted, halogen, acyl group that may be substituted, and amino group that may be substituted, for R^2, may each be the same as the substituents mentioned for the hydrocarbon or heterocyclic group for R. Preferably, R^2 is hydrogen, hydroxy group that may be substituted, or halogen. More preferably, R^2 is hydrogen or hydroxy group that may be substituted. Particularly preferred is hydrogen or a C_{1-4} alkoxy group.

L and M respectively represent hydrogen or may be combined with each other to form a chemical bond, and preferably they are hydrogen.

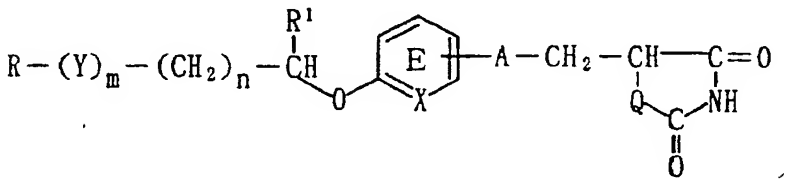
Referring to the formula (I), the compound in which L and M are combined with each other to form a chemical bond:



(I-A1)

wherein each symbols has the same meanings as defined above, may exist as (E)- and (Z)- isomers, owing to the double bond at 5-position of the azolidinedione ring.

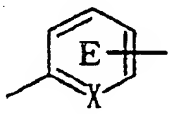
The compound in which L and M respectively represent hydrogen:



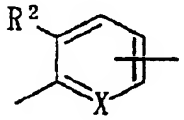
(I-A2)

wherein each symbols has the meanings as defined above, may exist as optical isomers, i.e. (R)- and (S)-forms, with respect to the asymmetric carbon at 5-position of the azolidinedione ring. This compound includes those optically active compounds, i.e. (R)- and (S)-forms, as well as the racemic form.

The preferred compound of the formula (I) is the compound in which R represents pyridyl, oxazolyl, or thiazolyl group, optionally having 1 to 3 substituents selected from the group consisting of C_{1-3} alkyl, furyl, thienyl, phenyl, and naphthyl; Y represents -CH(OH)- or $-NR^3-$ wherein R^3 is methyl; n is 0 or 1; X represents CH; A represents a chemical bond or $-(CH_2)_2-$; R^1 represents hydrogen; ring E, namely the partial structural formula:



is the formula:



wherein R^2 is hydrogen or a C_{1-4} alkoxy group; and L and M respectively represent hydrogen.

As preferred species of the compound of the formula (I), the following compounds are mentioned.

1) 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione;

2) 5-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-

oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione;
3) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione;
4) (S)-(-)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione;
5) 5-[3-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione;
6) 5-[5-[3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]pentyl]-2,4-oxazolidinedione;
7) 5-[3-[3,5-dimethoxy-4-[2-[(E)-styryl]-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione;
8) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione;
9) 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione.

Hereafter, these compounds are sometimes simply referred to as compound No.1, compound No.2, and the like.

Among the above compounds, compound Nos. 1, 3, 8 and 9 are preferred, and compound Nos.1 and 3 are particularly preferred.

The salt of compound (I) of the present invention is preferably a pharmacologically acceptable salt, which includes salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

The preferred salt with an inorganic base includes alkali metal salts such as sodium salt, potassium salt, etc.; alkaline earth metal salts such as calcium salt, magnesium salt, etc.; aluminum salt, and ammonium salts.

The preferred salt with an organic base includes salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,

dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.

The preferred salt with an inorganic acid includes salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

The preferred salt with an organic acid includes salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

The preferred salt with a basic amino acid includes salts with arginine, lysine, ornithine, etc. The preferred salt with an acidic amino acid includes salts with aspartic acid, glutamic acid, etc.

The most preferred of all the above-mentioned salts is hydrochloride, sodium salt or potassium salt.

Compound (I) or a salt thereof of the present invention can be produced in accordance with methods described in JP-A S55(1980)-22636 (EP-A-8203), JP-A S60(1985)-208980 (EP-A-155845), JP-A S61(1986)-286376 (EP-A-208420), JP-A S61(1986)-085372 (EP-A-177353), JP-A S61(1986)-267580 (EP-A-193256), JP-A H5(1993)-86057 (WO-A-9218501), JP-A H7(1995)-82269 (EP-A-605228), JP-A H7(1995)-101945 (EP-A-612743), EP-A-643050, EP-A-710659 (JP-A H9(1997)-194467), etc, or methods analogous thereto.

Compound (I) or a salt thereof of the present invention (hereinafter simply referred to as compound of the present invention) is useful as an anti-inflammatory agent which affects by way of a TNF-α inhibitory action. In addition, the toxic potential of the compound of the present invention is low. The TNF-α inhibitory action means reduction in the production amount of TNF-α in the living tissues (e.g., skeletal muscles, monocytes, macrophages, neutrophils, fibroblasts, epithelial cells, astrocytes, etc.) and reduction in the activity of TNF-α.

The anti-inflammatory agent of the present invention can be used as an agent for prophylaxis and treatment of TNF-α mediated inflammatory diseases in mammals (e.g., man, mouse, rat, rabbit, dog, cat, bovine, equine, swine, monkey, etc.). The TNF-α mediated inflammatory diseases mean inflammatory diseases which occur in the presence of TNF-α and can be treated by way of a TNF-α inhibitory action.

Examples of such inflammatory diseases include diabetic complications (e.g., retinopathy, nephropathy, neutropathy, disorders in the great arteries, etc.), rheumatoid arthritis, osteoarthritis of the spine, osteoarthritis, low back pain, gout, postoperative or traumatic inflammation, remission of swelling, neuralgia, laryngopharyngitis, cystitis, hepatitis, pneumonia, etc.

As the anti-inflammatory agent of the present invention, the compound of the present invention as such can be used. Usually, the anti-inflammatory agent is used in the form of a pharmaceutical composition obtained by formulating the compound of the invention with per se known pharmaceutically acceptable carriers.

As the pharmaceutically acceptable carrier, a variety of organic and inorganic carriers in common use as raw materials for pharmaceutical preparations are employed. The carrier is formulated in the form of the excipient, lubricant, binder, and disintegrator for a solid dosage form; and the solvent, solubilizer, suspending agent, isotonizing agent, buffering agent and local analgesic for a liquid dosage form. When necessary, pharmaceutical additives such as the preservative, antioxidant, coloring agent, sweetener, etc. can also be used.

The preferred excipient includes lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic anhydride, etc.

The preferred lubricant includes magnesium stearate, calcium stearate, talc, colloidal silica, etc.

The preferred binder includes crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, etc.

The preferred disintegrator includes starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, etc.

The preferred solvent includes water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, tricaprylin, etc.

The preferred solubilizer includes polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

The preferred suspending agent includes surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate, etc. and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

The preferred isotonizing agent includes sodium chloride, glycerin, D-mannitol, etc.

The preferred buffering agent includes buffer solutions such as phosphate, acetate, carbonate, citrate, etc.

The preferred local anesthetic includes benzyl alcohol, etc.

The preferred antiseptic includes p-hydroxybenzoic esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The preferred antioxidant includes salts of sulfurous acid, ascorbic acid, etc.

The above pharmaceutical composition can be manufactured by conventional methods in the pharmaceutical

preparation techniques, for example methods described in the Japanese Pharmacopoeia.

Examples of dosage forms of the pharmaceutical composition include oral dosage forms such as tablets, capsules (inclusive of soft capsules and microcapsules), powders, granules, and syrups; and non-oral dosage forms such as injections, suppositories, pellets, and drip infusions. These dosage forms can be safely administered either orally or non-orally.

The dosage of the anti-inflammatory agent of the present invention differs depending on the subject, route of administration, clinical condition, etc. For oral administration to an adult patient, for instance, the usual unit dose is about 0.1 mg/kg to about 30 mg/kg, preferably about 2 mg/kg to about 20 mg/kg, as the compound of the invention which is an active ingredient, which dose is preferably administered once to 3 times a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following examples and test examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention.

Example 1

A fluidized-bed granulating and drying machine (produced by powerex, Japan) was charged with 2479.5 g of hydrochloride of Compound No.1 (2250 g in terms of Compound No.1), 13930.5 g of lactose and 540 g of carboxymethylcellulose calcium (carmellose calcium), followed by mixing at the preheating temperature and spraying 7500 g of an aqueous solution containing 450 g of hydroxypropylcellulose to yield granules. 16820 g of the granules were processed with cutter-mill (produced by Showa Kagaku Kikai Kousakusho, Japan) to yield milled granules. 16530 g of the milled granules, 513 g of carmellose calcium and 57 g of magnesium stearate were mixed to yield

lubricated powders by using tumbling mixer (produced by Showa Kagaku Kikai Kousakusho, Japan). 16800 g of the lubricated powders were tabletted by using tabletting machine (produced by Kikusui Seisakusho, Japan) to yield 140000 tablets having the following formula and each containing 15 mg of Compound No. 1.

Formula per tablet (Unit: mg):

1) Hydrochloride of Compound No.1	16.53
2) Lactose	92.87
3) Carmellose calcium	7.2
4) Hydroxypropylcellulose	3.0
5) Magnesium stearate	0.4
Total:	120.0

Example 2

In substantially the same manner as in Example 1, 140000 tablets having the following formula and each containing 30 mg of Compound No.1 were obtained.

Formula per tablet (Unit: mg):

1) Hydrochloride of Compound No.1	33.06
2) Lactose	76.34
3) Carmellose calcium	7.2
4) Hydroxypropylcellulose	3.0
5) Magnesium stearate	0.4
Total:	120.0

Example 3

In substantially the same manner as in Example 2, 140000 tablets having the following formula and each containing 45 mg of Compound No.1 were obtained.

Formula per tablet (Unit: mg):

1) Hydrochloride of Compound No.1	49.59
2) Lactose	114.51
3) Carmellose calcium	10.8
4) Hydroxypropylcellulose	4.5
5) Magnesium stearate	0.6

Total: 180.0

Test Example 1 (Reduction of plasma TNF-α level in mice)

The plasma TNF-α level was determined by using KKA^y mice which are genetically obese, diabetic models, and a TNF-α inhibitory action of the compound of the present invention was evaluated.

Namely, eighteen male KKA^y mice (10 week old), genetically obese, diabetic models, were divided into two groups each of which consists of nine mice. A powdered commercial diet (CE-2, produced by Japan Clea) was given to one group (control group), and the above powdered diet also containing 0.001 %(w/w) of hydrochloride of Compound No. 1 was given to the other group (drug administration group) ad libitum. Mice in these groups were bred for 4 days. The average dosage of drug per mouse was 16 mg/kg body weight/day. On the fourth day, mice were sacrificed and blood was collected in tubes containing heparin.

The collected blood was centrifuged and the plasma TNF-α level was determined by the enzyme immunoassay based on the biotin-streptavidin method. Namely, 5 μl of a solution of an anti-TNF-α antibody IgG [produced by Genzyme, USA] (100 μg/ml) diluted with 0.05 M Tris-HCl buffer (pH 8.0) was added to each wells of a 96-well polystyrene microtiter plate [produced by Falcon, USA], followed by standing at the room temperature for 2 hours to adhere the anti-TNF-α antibody IgG to the plate. After removal of an excess antibody solution, each wells was washed with 0.1 M Tris-HCl buffer (pH 7.6) containing 0.4 M NaCl, 0.1 %(w/w) bovine serum albumin, 0.1 %(w/w) NaN_3 and 1 mM $MgCl_2$ (hereafter referred to as a washing buffer).

Ten μl of plasma or standard solution of TNF-α [Serotec, Great Britain] was added to each wells, followed by standing for 2.5 hours at the room temperature. After each wells was washed with a washing buffer, 200 μl of a solution of a biotinylated anti-TNF-α antibody IgG (35

ng/ml) diluted with a washing buffer was added, followed by standing over night at 4 ℃. After each wells was washed with a washing buffer, 20 μl of a solution of a β-D-galactosidase-linked streptavidin [produced by Boehringer Mannheim GmbH, Germany] diluted 6000 fold with a washing buffer was added, followed by standing for one hour at the room temperature.

Then, each wells was washed with a washing buffer, and β-D-galactosidase activity of an immune complex fixed at a solid phase was assayed. Namely, 30 μl of a substrate [60 mM of 4-methylumbelliferyl-β-D-galactoside, produced by Sigma, USA] was added to each wells to start an enzyme reaction. After the reaction was conducted at the room temperature for 4 hours, the enzyme reaction was stopped by addition of 0.13 ml of 0.1 M glycine-NaOH buffer (pH 10.3). The fluorescence intensity of the produced 4-methylumbelliferone was determined using a fluorescence spectrometer [Cyto Fluor II, PerSeptive Biosystems, USA] at the wavelengths of 350 and 460 nm for excitation and emission, respectively.

Then, the amount of TNF-α was calculated from the obtained fluorescence intensity using a separately prepared dose-response curve.

The results are shown in Table 1.

Table 1. Plasma TNF-α level (pg/ml)

Control group	Drug administration group (Present invention)
4.97±1.75	1.52±1.08**

Mean ± Standard Deviation; Significantly different from Control group (**:$p<0.01$)

It is apparent from Table 1 that the compound of the present invention significantly reduced plasma TNF-α level in mice.

Test Example 2 (Reduction of plasma TNF-α level in rats)

The plasma TNF-α level was determined by using Wistar fatty rats which are genetically obese, diabetic models, and a TNF-α inhibitory action of the compound of the present invention was evaluated.

Namely, hydrochloride of Compound No. 1 was orally administered to sixteen male Wistar fatty rats (16 week old), genetically obese, diabetic models, via gastric tube at a dose of 3 mg/kg body weight/day. Ten rats were sacrificed before drug administration, and the first, second, third and fourth day after drug administration, respectively. Then, blood was collected.

As the normal group, ten Wistar lean rats (16 week old) were sacrificed without drug administration and blood was collected.

The collected blood was centrifuged, and the plasma TNF-α level was determined in substantially the same manner as in Test Example 1.

The results are shown in Table 2.

Table 2. Plasma TNF-α level (pg/ml)

	Days after drug administration	TNF-α level (pg/ml)
Normal group	0	56.9±47.5
Control group	0	139.5±50.0
Present invention	1	109.9±61.0
	2	115.1±59.0
	3	69.9±64.3
	4	67.2±70.6*

Mean ± Standard Deviation; Significantly different from Control group (*:$p<0.05$)

It is apparent from Table 2 that the compound of the present invention reduced the plasma TNF-α level in rats time-dependently.

Test Example 3 (Reduction of TNF-α content in skeletal muscle of rats)

The TNF-α content in skeletal muscle was determined by using Wistar fatty rats which are genetically obese, diabetic models, and a TNF-α inhibitory action of the compound of the present invention was evaluated.

Namely, hydrochloride of Compound No. 1 was administered to male Wistar fatty rats (16 week old), genetically obese, diabetic models in substantially the same manner as in Test Example 2. Ten rats were sacrificed before drug administration, and the first, second, third and fourth day after drug administration, respectively. Then, skeletal muscle was collected.

As the normal group, ten Wistar lean rats (16 week old) were sacrificed without drug administration and skeletal muscle was collected.

To the collected skeletal muscle, 0.1 M Tris-HCl buffer (pH 7.6) containing 1 M NaCl, 2 %(w/w) bovine serum albumin, 2 mM ethylenediaminetetraacetic acid disodium salt (EDTA), aprotinin (80 tripsin-inhibitory units/liter) and 0.02 %(w/w) NaN_3 was added in an amount of 20 weight times of the weight of the wet skeletal muscle. After ultrasonic disintegration, the mixture was centrifuged at 15000 rpm for 30 minutes to obtain a supernatant.

The amount of TNF-α in the obtained supernatant was determined in substantially the same manner as in Test Example 1.

The results are shown in Table 3.

Table 3. TNF-α content in skeletal muscle (pg/g wet weight)

	Days after drug administration	Amount of TNF-α (pg/g wet weight)
Normal group	0	156.7± 61.9
Control	0	356.6±105.6

group		
Present	1	200.1±165.1*
invention	2	181.4±108.2**
	3	105.1± 96.4**
	4	107.3± 95.7**

Mean ± Standard Deviation; Significantly different from Control group (*:$p<0.05$, **:$p<0.01$)

It is apparent from Table 3 that the compound of the present invention reduced the TNF-α content in skeletal muscle of rats significantly and almost time-dependently.

Test Example 4 (Suppression of the active oxygen production in neutrophils)

The in vitro effect of the compound of the present invention on suppression of the active oxygen production in neutrophils was evaluated by determining the amount of peroxides in cells.

Namely, venous blood was collected from male Wistar rats (6 week old) while adding heparin. To the collected blood, the same volume of an aqueous solution of 3 %(w/w) dextran was added for separation of blood cells. After the mixture was allowed to stand for 30 minutes, precipitates obtained by centrifugation was suspended with saline. The suspension was piled on Ficoll-Hypaque solution (Sigma, USA), followed by centrifugation.

From the obtained precipitates, erythrocytes were removed by hemolysis to separate neutrophils.

The hemolysis was conducted in the following manner. Namely, 4 ml of an ice-cooled 0.2 %(w/w) aqueous solution of NaCl was added to the above precipitates, which was suspended quickly, followed by standing for 20 to 30 seconds to puncture the erythrocytes. Then, 4 ml of an ice-cooled 1.6 %(w/w) aqueous solution of NaCl was added to the obtained suspension, which was mixed to yield a mixed solution having the same osmotic pressure with the erythrocytes before puncture. The mixed solution was

centrifuged at 4 ℃ at 150 × g for 5 minutes. After the supernatants were removed, the precipitates were washed with PBS (phosphate buffer saline).

The thus obtained erythrocytes were washed with saline, followed by addition of a minimum essential medium to prepare a neutrophils floating solution. The obtained neutrophils floating solution was fractionated into tubes so that the number of neutrophiles per tube is 106.

Then, hydrochloride of Compound No. 1 or Compound No. 8 was added to the obtained tubes at the concentration of 1 μM. After incubation for one hour, a fluorescent pigment [DCFH-DA (2,7-dichlorofluoresceine diacetic acid)] was added, which was subjected to determination of the fluorescence intensity by FACScan (Becton Dickinton, USA).

As the control group, the fluorescence intensity in the case of adding no drug was determined.

The relative values of the fluorescence intensity in the drug addition group when the fluorescence intensity in the control group was 100 were calculated. These values were defined as the amount of peroxides caused by active oxygen derived from neutrophils.

The results are shown in Table 4.

Table 4. Fluorescence intensity and peroxide level

	Fluorescence intensity	Peroxide level
Control group	707	100
Hydrochloride of Compound No. 1 (Present invention)	466	66
Control group	377	100
Hydrochloride of Compound No. 8 (Present invention)	242	64

It is apparent from Table 4 that the compound of the present invention suppressed the active oxygen production

in neutrophils.

TNF-α is produced by various cells such as monocytes, macrophages, neutrophils, fibroblasts, epithelial cells, astrocytes, and etc. TNF-α increases production of active oxygen in neutrophils, which are suggested to have a close relation with occurrence of rheumatoid arthritis [Clinical and Experimental Rheumatology, vol. 15, pp.233-237 (1997); Inflammation, vol. 20, pp.427-438 (1996)].

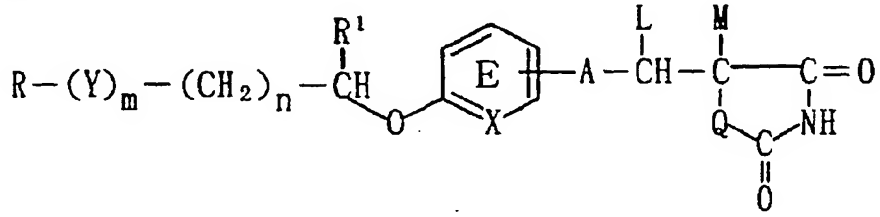
Therefore, it is considered that the compound of the present invention exhibited suppressive effects on the active oxygen production by reducing TNF-α production or TNF-α sensitivity in neutrophils based on the results of Test Example 4.

Industrial Applicability

The anti-inflammatory agent of the present invention is used as an agent for prophylaxis and treatment of TNF-α mediated inflammatory diseases such as diabetic complications (e.g., retinopathy, nephropathy, neutropathy, disorders in the great arteries, etc.), rheumatoid arthritis, osteoarthritis of the spine, osteoarthritis, low back pain, gout, postoperative or traumatic inflammation, remission of swelling, neuralgia, sore throat, cystitis, hepatitis, pneumonia, and etc.

CLAIMS

1. An anti-inflammatory agent which affects by way of a TNF-α inhibitory action and comprises a compound of the formula:



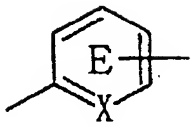
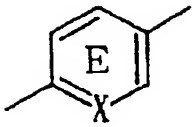
wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula -CO-, -CH(OH)-, or $-NR^3-$ where R^3 represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R^1 represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R^1; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond; or a salt thereof.

2. An anti-inflammatory agent according to Claim 1, wherein the heterocyclic group represented by R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen in addition to carbon as ring members or a condensed heterocyclic group.

3. An anti-inflammatory agent according to Claim 1, wherein R represents a heterocyclic group that may be substituted.

4. An anti-inflammatory agent according to Claim 3, wherein the heterocyclic group is pyridyl, oxazolyl or thiazolyl.

5. An anti-inflammatory agent according to Claim 1, wherein the partial structural formula:

 is the formula: 

6. An anti-inflammatory agent according to Claim 1, wherein X represents CH.

7. An anti-inflammatory agent according to Claim 1, wherein R^1 represents hydrogen.

8. An anti-inflammatory agent according to Claim 1, wherein L and M respectively represent hydrogen.

9. An anti-inflammatory agent according to Claim 1, wherein the compound is 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

10. An anti-inflammatory agent according to Claim 1, wherein the compound is (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione.

11. Method for treating or preventing a TNF-α mediated inflammatory disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound as defined in claim 1 or a pharmacologically acceptable salt thereof.

12. Use of a compound as defined in claim 1 or a pharmacologically acceptable salt thereof for the manufacture of an agent for prophylaxis or treatment of a TNF-α mediated inflammatory disease.

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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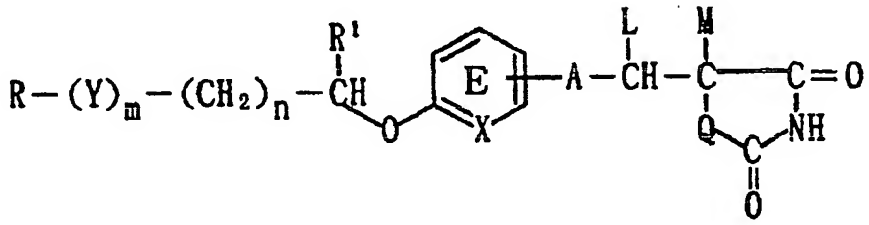

(I)

(57) Abstract

An anti–inflammatory agent which affects by way of a TNF–α inhibitory action and comprises a compound of formula (I) wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula –CO–, –CH(OH)–, or –NR^3– where R^3 represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R^1 represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R^1; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond or a salt thereof.

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INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/JP 98/03692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/42 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R.W.STEVENSON ET AL.: "The thiazolidinedione drug series" THE DIABETES ANNUAL, vol. 9, 1995, pages 175-191, XP002094463 see page 185 - page 186 ---	1-12
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1999	09/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Theuns, H

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/JP 98/03692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	D.SZALKOWSKI ET AL.: "Antidiabetic Thiazolidinediones Block the Inhibitory Effect of Tumor Necrosis Factor-alpha on Differentiation, Insulin-Stimulated Glucose Uptake, and Gene Expression in 3T3-L1 Cells" ENDOCRINOLOGY, vol. 136, no. 4, April 1995, pages 1474-1481, XP002094465 see abstract	1-12
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INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/JP 98/03692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 98/03692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
See FURTHER INFORMATION SHEET PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP 98 /03692

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been based on the alleged effects of the compound/composition. In view of the large number of compounds comprised by the formula of claim 1 the search has been restricted to the general concept underlying the application and the specific compounds mentioned in the claims.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/JP 98/03692

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